50. (Amended) The kit of claim 44, wherein the package housing further comprises a second container containing a medicament other than the compound for the treatment of a cardiovascular disease, and wherein the instructions are for using the compound and the medicament to treat the cardiovascular disease.

B7

51. (Amended) The kit of claim 50, wherein the medicament for the treatment of the cardiovascular disease is a medicament for the treatment of hypertension.

53. (Amended) The kit of claim 50, wherein the medicament for the treatment of the cardiovascular disease is a medicament for the treatment of angina.

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54. (Amended) The kit of claim 44, wherein the package housing further comprises a second container containing a medicament for the treatment of a migraine disorder, and wherein the instructions are for using the compound and the medicament to treat the migraine disorder.

Please cancel claims 38 and 52.

REMARKS

Claims 20-37, 39-51, 53, and 54 are pending. Claims 21 and 23 to 26 have been allowed. Claims 20, 22, 27, 35, 36, 38, 40, 42, and 44 to 54 have been rejected. Claims 28 to 34, 37, 39, 41, and 43 have been objected to. Applicants have amended claims 22, 29, 35, 38, 40, 42, 44, 45, and 50 to 54. No new matter is presented.

The Examiner has not returned the PTO-1449 form provided by Applicants in an Information Disclosure Statement dated March 11, 2002. Applicants request that the Examiner consider the cited information and sign and return the PTO-1449 form. Additionally, Applicants submit herewith an additional Information Disclosure Statement explicitly citing the references the Examiner provided in the Office Action dated March 13, 2002.

Applicants have amended claim 29 and deleted claims 38 and 52 to remove the claimed methods and kits related to treating congestive heart failure. Applicants reserve the right to pursue these claims in this or a continuing application.

Claim Objections

Claims 28 to 34, 37, 39, 41, and 43 were objected to as being dependent upon a rejected base claim. The Examiner indicated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants have chosen not to rewrite these claims in independent form at this time, but reserve the right to do so in this or a continuing application.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 27 and 44 were rejected under 35 U.S.C. § 112, first paragraph, as being not enabled for the treatment of other types of disorders associated with calcium channel activity that were not explicitly named in the specification. Applicants respectfully traverse this rejection.

Applicants provide *in vitro* data in Example 2 (page 44, line 1, to page 45, line 10) and *in vivo* data in Example 3 (page 45, line 12, to page 46, line 18) from analyses of test compounds for calcium channel blocking activity. The compounds were compared to the known calcium channel blocker diltiazem. In each case, the compounds of the invention caused a significant reduction in maximal arterial blood pressure (indicative of calcium channel blockage) as compared to diltiazem and to a control.

Calcium channels are well studied in the art, and disorders associated with calcium channel activity are well characterized. Applicants have provided an extensive list of disorders associated with calcium channel activity. The rejected claims are directed to treating disorders which have been established as associated with calcium channel activity. Such disorders are not limited to those disclosed in the specification but encompass presently known disorders established to be associated with calcium channel activity and even future disorders once they are established to be associated with calcium channel activity.

Accordingly, Applicants believe claims 27 and 44 are enabled and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 22 and 45 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants have amended claims 22 and 45 to be in one sentence form only by adding a period to complete the sentences. This amendment does not affect the scope of the claims. Accordingly, applicants request the withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Claims 35, 36, 38, 40, 42, and 50 to 54 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants have amended claims 35, 40, 42, and 50 to 54 to clarify the subject matter which Applicants regard as the invention. These amendments do not affect the breadth of the claim scope. Claims 38 and 52 have been cancelled and therefore the rejection with respect to these claims is moot. Accordingly, Applicants believe claims 35, 36, 40, 42, and 50 are definite, and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. § 101

Claims 35, 36, 38, 40, 42, and 50 to 54 were rejected under 35 U.S.C. § 101, as being not proper process claims. As stated above, Applicants have amended claims 35, 40, 42, 50, 51, 53, and 54 and cancelled claims 38 and 52. Applicants believe these amendments clarify the claimed methods in claims 35, 36, 40, and 42. Applicants would like to point out that claims 50 to 54 are directed to kits, and as such, the rejection under 35 U.S.C. § 101 as not being a proper process claim is improper. Accordingly, Applicants believe the claims are in condition for allowance, and withdrawal of the rejection under 35 U.S.C. § 101 is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

Claim 20 was rejected under 35 U.S.C. § 103 (a) as being unpatentable over Gialdi (Gialdi, *et al.* Abstract to CA 56:4664g) in view of McMurry (McMurry, *ed.*, Organic Chemistry, 1984, pp. 742-746). Applicants respectfully traverse this rejection.

Gialdi discloses compounds with two phenyl rings linked by $-S-CH_2-$ with an amide group at the ortho position. Although it is known to transform acyl chloride groups into amide groups, Gialdi and McMurry, alone or in combination, provide no motivation to synthesize the compound claimed in claim 20. The Examiner seems to suggest that in hindsight, it is obvious to form an acyl chloride intermediate to make the amide compounds of the invention. But, that is not the test for obviousness. The teaching or suggestion to make the claimed combination must both be found in the prior art, and not based on Applicants' disclosure. (*In re Baeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Accordingly, . Applicants believe that claim 20 is not obvious and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Additionally, the Examiner provided two Jilek references, Chemical Abstracts Accession No. 1992:612134 and 1990:458596, along with the Gialdi reference in the Office Action. (The two Jilek references are provided herewith by Applicants in an Information Disclosure Statement.) The two Jilek

references disclose compounds with two phenyl rings linked together via a sulfur bond. However, the two Jilek references lack the methylene moiety in between the two phenyl groups as recited in claim 20. As stated above, although it is known to transform acyl chloride compounds into amide compounds, the two Jilek references alone, or in combination with Gialdi or McMurry, provide no motivation to make the compounds recited in claim 20.

Claims 44 to 54 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Gialdi. The Examiner states that Applicants attempt to limit claims 44 to 54 with the incorporation of an intended use, which must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention and the prior art. Further, the Examiner states that, if the prior art structure is capable of performing the intended use, then it meets the claim. Applicants respectfully traverse this rejection.

The rejected claims are directed to kits. These kits comprise a package housing a container containing a compound to inhibit calcium channels, a pharmaceutically acceptable carrier and instructions for use. In claims 50, 51, 53, and 54, the kits further comprise a second container containing a medicament (other than the compound) for the treatment of cardiovascular disease. Applicants have amended claim 44 to remove the words "in an amount effective." Applicants have made this amendment to broaden the claim, for example, to encompass kits wherein the compound is provided in an amount more concentrated or more diluted than an amount effective to inhibit calcium channels. Claim 44 has also been amended to correct a typographical error and to recite proper Markush group language.

Gialdi, discussed above, does not teach or suggest any use of the disclosed compounds, much less using them in a kit to inhibit calcium channels, or to include in the kit instructions for use for the inhibition of calcium channels. Further, Gialdi does not teach or suggest a kit comprising the claimed compounds along with a second container containing a medicament (other than the claimed compounds) for the treatment of a cardiovascular disease or a migraine disorder, as recited in the instant claims. Accordingly, Applicants believe the rejected claims are not obvious over Gialdi and withdrawal of the rejection is respectfully requested.

Applicants believe that the rejected claims are not obvious in light of the two Jilek references. The first Jilek Abstract (1992:612134) teaches a group of compounds useful as anti-microbial agents and intermediates inserted in the preparation of antimicrobial agents. The second Jilek reference (1990:458596) teaches a class of compounds that are potentially useful as antidepressants. Neither of the two Jilek references teach or suggest using the claimed compounds in a kit to inhibit calcium channels, or to include in the kit instructions for use for the inhibition of calcium channels. Further, neither Jilek

reference teaches or suggests a kit comprising the claimed compounds along with a second container containing a medicament (other than the claimed compounds) for the treatment of a cardiovascular disease or a migraine disorder, as recited in the instant claims. As a result, Applicants believe that the rejected claims are not obvious over the two Jilek references and an indication of allowance is respectfully requested.

Claims 44 to 54 were rejected under 35 U.S.C. § 103 (a) over Gialdi in view of McMurry. Applicants respectfully traverse this rejection. The Examiner states that the difference between Gialdi and the instant invention is that the instant invention has an ortho carboxylic acid halide moiety, whereas Gialdi, teaches a carboxylic acid amide moiety in the ortho position. The Examiner cites McMurry to teach the reactivates of carboxylic acid derivatives. Further, the Examiner states ("[a]lthough Hart states that amides cannot be converted into acid halides, McMurry do [*sic*] provide motivation to have a more reactive carboxylic acid derivative group...") on page 6 of the outstanding Office Action. The Examiner has not provided the Hart reference and Applicants respectfully request that the Examiner provide the Hart reference if he intends to maintain this rejection.

The rejected claims are directed to kits comprising the compounds of the invention to inhibit calcium channels. The kits further comprise instructions for using the compounds to treat subjects having calcium channel blocking disorders.

As stated above, the Gialdi reference does not teach or suggest the compounds of the invention, much less kits comprising the compounds of the invention and instructions for their use. Withdrawal of the rejection under 35 U.S.C. § 103 (a) is respectfully requested.

In addition, Applicants assert that the rejected claims are patentable in view of the two Jilek references, alone or in combination with Gialdi and McMurry. The two Jilek references disclose compounds that are useful as antimicrobial agents against *Pseudomonas aeruginosa, Proteus vulgaris*, and *Trichophyton mentagrophytes* and as potential antidepressants. The two Jilek references do not teach or suggest kits, or kits comprising the compounds of the invention to treat subjects having a calcium channel blocking disorder.

Applicants believe that in view of the amendments to the claims, and the remarks above, claims 20 to 37, 39-51, 53, and 54 are in condition for allowance. Such action is respectfully requested.

If the Examiner wishes to advance prosecution in any way, or if the Amendment is unclear, then the Examiner is invited to call the undersigned at the telephone number listed below.

Respectfully Submitted,

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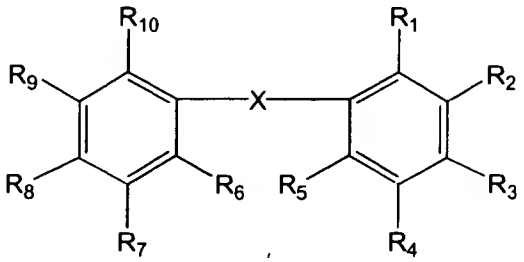
Docket No. M00966/70001(HCL/CMD)
Date: August 8, 2002
xxAugust 13, 2002

MARKED-UP CLAIMS

22. (Amended) The method of claim 21, wherein the compound has the general structural formula:



29. (Amended) The method of claim 28, wherein the cardiovascular disease is selected from the group consisting of hypertension, [congestive heart failure,] arrhythmia, and angina.

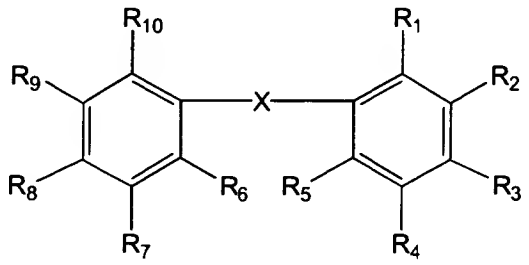
35. (Twice Amended) The method of claim 27, further comprising administering to the subject a medicament other than the compound in an amount effective to treat a [for the treatment of] cardiovascular disease.

40. (Amended) The method of claim 35, wherein the medicament is administered in an amount effective to treat [for treating] angina.

42. (Amended) The method of claim 35, wherein the medicament is administered in an amount effective to treat [for treating] arrhythmia.

44. (Amended) A kit comprising:

- a package housing a container containing a compound [in an amount effective] to inhibit calcium channels and a pharmaceutically acceptable carrier, wherein the compound has the general structural formula:



wherein R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9, and R_{10} independent of one another, are selected from the group consisting of -H, halogen, piperonyl, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_1-C_6) alkoxy, -CN, -OR', -SR', -NO_2, -NR'R', amino acid, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR, -C(S)SR', -C(O)N(R')$_2$, -C(O)C(O)R', -C(S)C(O)R', -C(O)C(S)R', -C(S)C(S)R', -C(O)C(O)OR', -C(S)C(O)OR', -C(O)C(S)OR', -C(O)C(O)SR', -C(S)C(S)OR', -C(S)C(O)SR', -C(O)C(S)SR', -C(S)C(S)SR', -C(O)C(O)N(R')$_2$, -C(S)C(O)N(R')$_2$, -C(O)C(S)N(R')$_2$, [or] and -C(S)C(S)N(R')$_2$;

wherein R_6 is in the ortho position and is selected from the group consisting of -CO-NH-$(CH_2)_{2\text{-}5}NH_2$, -CO-NH-$(CH_2)_{2\text{-}5}$NH-$(CH_2)_z$-H, -CO-NH$(CH_2)_{2\text{-}5}NR_{15}(CH_2)_z$-H, -CO-R', -CO-OR', -CO-SR', -CO-N(R')$_2$, -CO-CO-R', -CO-CS-R', -CO-CO-OR', -CO-CS-OR', -CO-CO-SR', -CO-CS-SR', -CO-CO-N(R')$_2$, -CO-CS-N(R')$_2$, -NH-CO-NH-$(CH_2)_{2\text{-}5}NH_2$, -NH-CO-NH-$(CH_2)_{2\text{-}5}$NH-$(CH_2)_z$-H, -NH-CO-NH$(CH_2)_{2\text{-}5}NR_{15}(CH_2)_z$-H, -NH-CO-R', -NH-CO-OR', -NH-CO-SR', -NH-CO-NO_2, -NH-CO-N(R')$_2$, -NH-CO-CO-R', -NH-CO-CS-R', -NH-CO-CO-OR', -NH-CO-CS-OR', -NH-CO-CO-SR', -NH-CO-CS-SR', -NH-CO-CO-N(R')$_2$, and -NH-CO-CS-N(R')$_2$,

wherein each R' is $(CH_2)_z$ -NR"R" and wherein R" is independently selected from the group consisting of (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkoxy, (C_1-C_6) alkynyl, (C_6-C_{20}) aryl, (C_6-C_{20}) substituted aryl, (C_6-C_{26}) alkaryl, substituted (C_6-C_{26}) alkaryl, and (C_5-C_7) heteroaryl wherein at least one atom of the heteroaryl is selected from the group consisting of a sulfur, a nitrogen, [or] and an oxygen atom, wherein the aryl and alkaryl substituents are each independently selected from the group consisting of hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl and trihalomethyl;

wherein z is 1-6;

wherein R_{15} is selected from the group consisting of halogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, and (C_1-C_6) alkoxy;

wherein X is a group having the following formula;

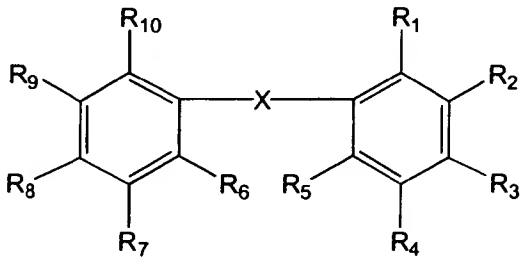
$$-(CH_2)_m\text{-}Y\text{-}(CH_2)_n-$$

wherein Y is selected from the group consisting of S, N, and O;

wherein m and n, independent of one another, are integers of 0-5; and,

- instructions for using the compound to treat a subject having a calcium channel blocking disorder.

45. (Amended) The kit of claim 44, wherein the compound is of the general formula:



50. (Amended) The kit of claim 44, wherein the package housing further comprises [comprising] a second container containing a medicament other than the compound for the treatment of a cardiovascular disease, and wherein the instructions are for using the compound and the medicament to treat the cardiovascular disease.

51. (Amended) The kit of claim 50, wherein the medicament for the treatment of the cardiovascular disease is a medicament for the treatment of hypertension.

53. (Amended) The kit of claim 50, wherein the medicament for the treatment of the cardiovascular disease is a medicament for the treatment of angina.

54. (Amended) The kit of claim 44, wherein the package housing further comprises [comprising] a second container containing a medicament for the treatment of a migraine disorder, and wherein the instructions are for using the compound and the medicament to treat the migraine disorder.